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## CONVENIENT METHODS FOR THE SYNTHESIS OF NOVEL THIADIAZOLES AND POLYTHIADIAZOLES

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**Abstract** – In this study, the novel thiadiazoles were formed via the reaction of hydrazoneyl halides with methyl 2-(adamantan-2-ylidene)hydrazinecarbodithioate. Also, the reaction of 2,5-dihydrazinyl-1,3,4-thiadiazoles with 2-adamantanone or acetylferrocene produced the 2,5-bis(2-(adamantan-2-ylidene)hydrazinyl)-1,3,4-thiadiazole or 2,5-bis(2-(1-(ferrocenylidene)hydrazinyl)-1,3,4-thiadiazole, respectively. Analogously, treatment of terephthalaldehyde with 2,5-dihydrazinyl-1,3,4-thiadiazole afforded new poly(benzylidenehydrazinyl-1,3,4-thiadiazole). Finally, the reaction of bishydrazoneyl halides with 2,5-dihydrazinyl-1,3,4-thiadiazole afforded new poly(1,3,4-thiadiazolo[2,3-*c*][1,2,4]triazine). The synthetic structures for the final products are suggested and discussed. The compound structures of the products were recognized by different spectroscopic analyses.

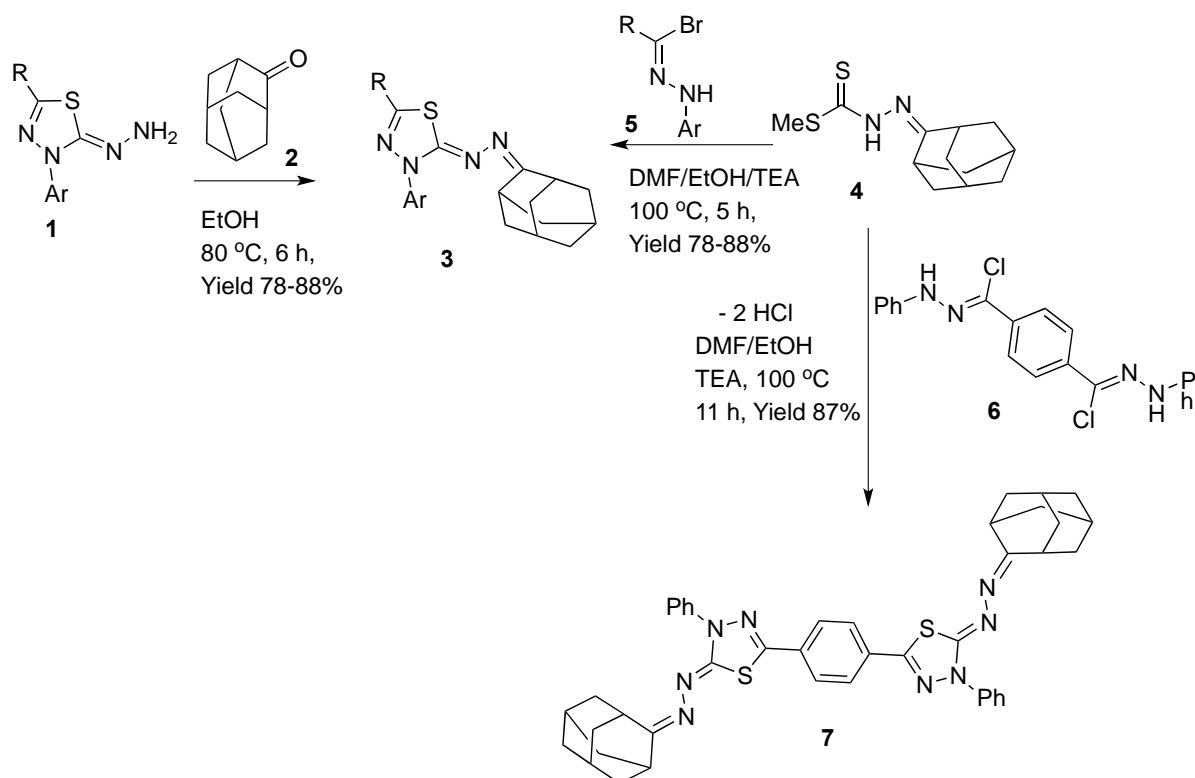
The importance in the chemistry of hydrazoneyl halides is an impact of the fact that they carry out different variety of reactions, which afford methods to several of heterocyclics.<sup>1-4</sup> Thiadiazoles are important heterocyclic organic materials with full range of biological accomplishments for example, antiviral,<sup>5</sup> anticancer,<sup>6</sup> and anti-inflammatory<sup>7</sup> and antimicrobial.<sup>8</sup> Thiadiazoles containing trifluoromethylated prepared via the regioselective [3+2] cycloadditions of fluorinated hydrazoneyl halides with different thione compounds.<sup>9</sup>

Ferrocene has attracted a great attention in bioorganic chemistry because they are nontoxic and have good redox properties. Ferrocenyl materials show remarkable performance when used as antitumor, antimalarial, antifungal agents and in DNA-cleaving activity.<sup>10,11</sup> In addition, adamantane has been used in some dry etching masks<sup>12</sup> as antiviral drug against various strains of flu<sup>13</sup> and polymers containing

adamantane have been patented as antiviral agents against HIV.<sup>14</sup>

Herein, we synthesized novel thiadiazoles, poly(benzylidenehydrazinyl-1,3,4-thiadiazole) and poly(1,3,4-thiadiazolo[2,3-*c*][1,2,4]triazine). The compound structures of the products were recognized by different spectroscopic analyses.

The new thiadiazoles described in this manuscript with different functional groups to produce novel compounds with interesting properties based on hydrazoneyl halides. This work is a continuation of our active research in the area of hydrazoneyl halides and their reactions with different moieties, reported in.<sup>15,16</sup> We present the reaction of 2-adamantanone **2**<sup>17</sup> with the 2-hydrazinyl-1,3,4-thiadiazoline derivatives **1**<sup>18</sup> in ethanol under reflux to produce the final product 2-(adamantan-2-ylidenehydrazono)-3-substituted aromatic-5-substituted aromatic-2,3-dihydro-1,3,4-thiadiazole **3**. The final products were elucidated by elemental analysis and spectral data as mentioned in experimental part (Scheme 1). The compound **3** was further elucidated by alternated synthesis route via the reaction of hydrazoneyl bromide derivatives **5** with methyl hydrazinecarbodithioate **4** in boiling ethanol/dimethylformamide (DMF) and in the presence of basic medium to yield the final products of thiadiazoles **3**. The results obtained for synthesis of the compounds **3** in terms of (mp, mixed mp, and spectra) (Scheme 1) are identical with the same results obtained for the same compound when synthesized from the reaction of **4** with **5**.<sup>19</sup>

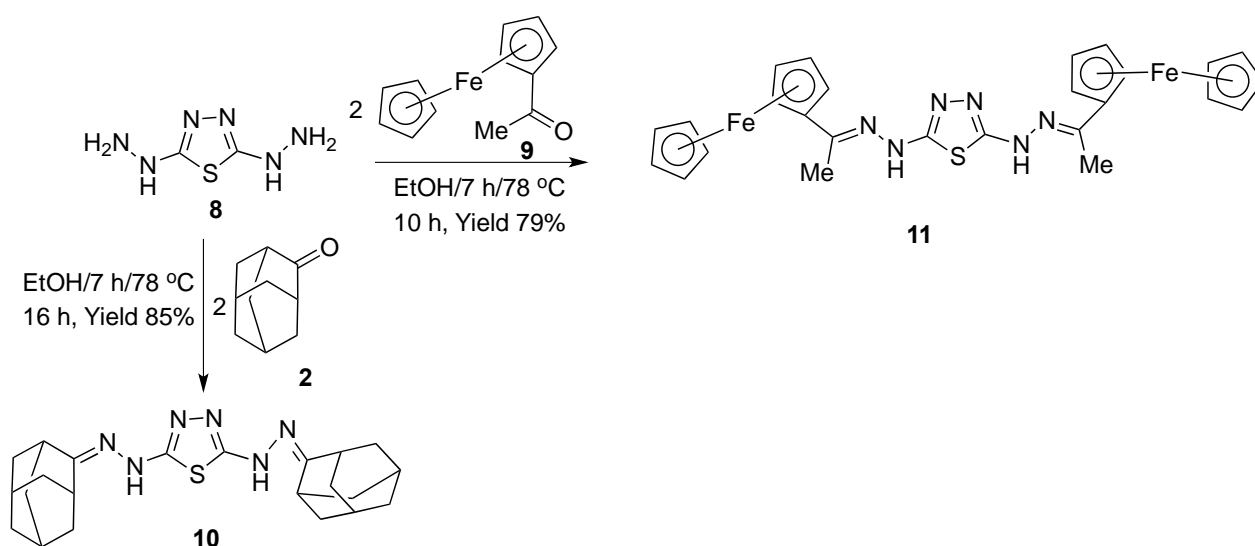


R: a, 4-MeOC<sub>6</sub>H<sub>4</sub>; b, 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>; c, C<sub>6</sub>H<sub>5</sub>; d, 4-ClC<sub>6</sub>H<sub>4</sub>; e, 4-BrC<sub>6</sub>H<sub>4</sub>  
Ar = 4-BrC<sub>6</sub>H<sub>4</sub>

**Scheme 1.** Synthesis of novel 1,3,4-thiadiazoles **3** and **7**

Analogously, treatment of 1,4-diphenylterephthalohydrazonoyl dichloride **6**<sup>20</sup> with methyl 2-(adamantan-2-ylidene)hydrazinecarbodithioate **4**<sup>19</sup> in ethanol/DMF and in the presence of triethylamine acting as a base under reflux gave 1,4-bis(5-(adamantan-2-ylidenehydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)benzene **7** in a good yield as depicted in Scheme 1. The final products gave a satisfactory elemental analysis and spectroscopic data (IR, NMR, and MS) consistent with the proposed structure for the compound **26** (Scheme 3). The IR spectra of products **7** indicated the absence of secondary amine group at  $3300\text{ cm}^{-1}$  (NH).

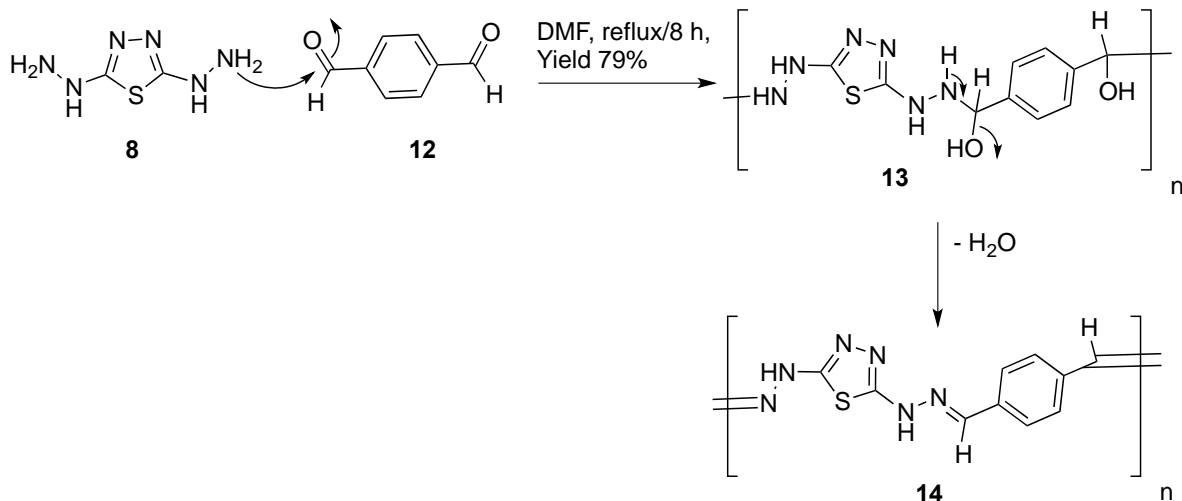
In addition, the reaction of 2,5-dihydrazinyl-1,3,4-thiadiazoles **8** with 2-adamantanone **2** or acetylferrocene **9** in ethanol under reflux produced the final products 2,5-bis(2-(adamantan-2-ylidene)hydrazinyl)-1,3,4-thiadiazole **10** or 2,5-bis(2-(1-(ferrocenylidene)hydrazinyl)-1,3,4-thiadiazole **11**, respectively. The compounds **10** or **11** have been obtained in a good yield (Scheme 2). The newly prepared compounds **10** or **11** were elucidated by elemental analysis and spectral data. The obtained data, showed in the experiment part, are compatible with the proposed structures for these compounds. For example, the IR spectrum **10** or **11** showed no absorption bands at  $1850\text{-}1650\text{ cm}^{-1}$  which is characteristic of C=O group and this confirmed the eliminated of water to form hydrazones **10** or **11**. <sup>1</sup>H NMR of the compounds **11** have signals at  $\delta$  2.51 (s, 6H, 2CH<sub>3</sub>), 4.12 (m, 10H, 2C<sub>5</sub>H<sub>5</sub>), 4.69 (m, 8H, 2C<sub>5</sub>H<sub>4</sub>), and 10.88 (s, 2H, NH) ppm.



**Scheme 2.** Synthesis of novel 1,3,4-thiadiazoles **10** and **11**

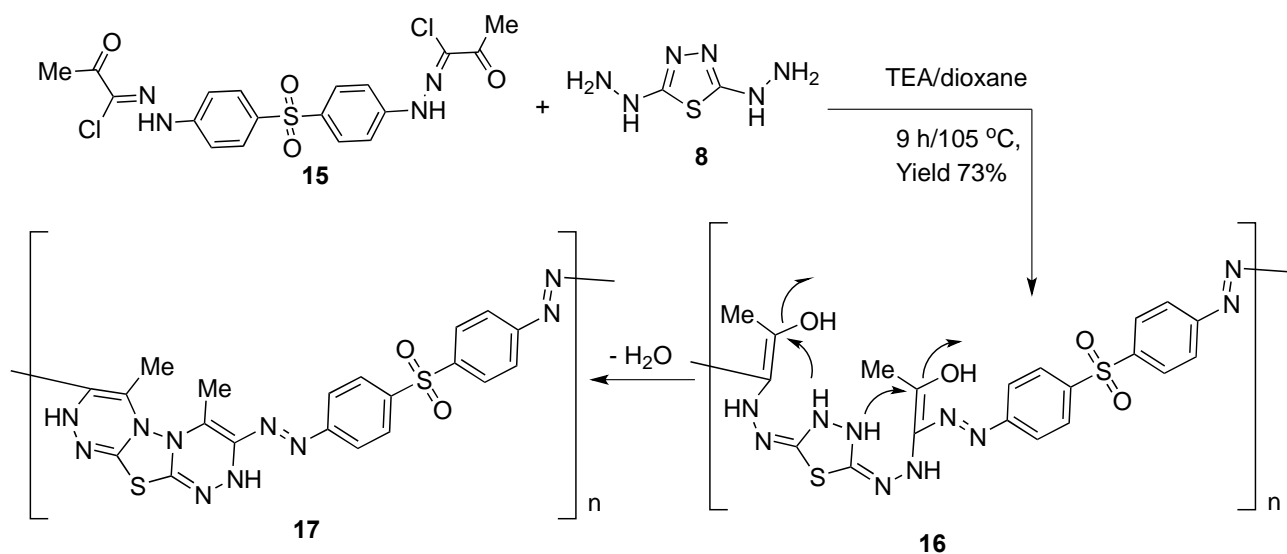
Reaction of terephthalaldehyde **12** with 2,5-dihydrazinyl-1,3,4-thiadiazole **8** in DMF under reflux afforded new poly(benzylidenehydrazinyl-1,3,4-thiadiazole) **14**. The reaction can be explained on the

basis of nucleophilic addition of hydrazinyl to carbonyl compounds of aldehydic followed by polycondensation via elimination of water molecules as depicted in Scheme 3. The molecular weight of the polymer could not be recorded owing to poor solubility.



**Scheme 3.** Synthesis of novel poly(benzylidenehydrazinyl-1,3,4-thiadiazole) **14**

Pleasingly, bishydrazonoyl halides **15** react with 2,5-dihydrazinyl-1,3,4-thiadiazole **8** in dioxane and in the presence of triethylamine as a base catalyst under reflux conditions proceeded smoothly to afford new poly(1,3,4-thiadiazolo[2,3-*c*][1,2,4]triazine) **17**; it is suggested that the reaction starts with the formation of hydrazide **16** followed by cyclization to give the product **17** via elimination of water molecules as depicted in Scheme 4. The <sup>13</sup>C NMR spectrum and molecular weight of the polymer could not be recorded owing to poor solubility.



**Scheme 4.** Synthesis of novel poly(1,3,4-thiadiazolo[2,3-*c*][1,2,4]triazine) **17**

## CONCLUSION

In summary, the studied reactions provide a facile new route for synthesized efficient synthesis of novel thiadiazoles, poly(benzylidenehydrazinyl-1,3,4-thiadiazole) and poly(1,3,4-thiadiazolo[2,3-*c*][1,2,4]triazine) by using a simple, mild, cost effective and environmentally benign reaction. The compound structures of the products were recognized by different spectroscopic data.

## EXPERIMENTAL

All the substances were purchased from Aldrich and Fulka and used without extra purification. Melting points were measured on an electrothermal Gallenkamp melting point apparatus and are uncorrected. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{DMSO-}d_6$  with tetramethylsilane (TMS) as an internal standard using 300 MHz Varian Gemini spectrometer. The IR spectra were measured on a Fourier Transform and Pye Unicam Infrared spectrophotometers by potassium bromide wafer. Mass spectra were recorded on a GCMS-QP 1000 EX spectrometer at an ionizing potential of 70 eV. Electronic absorption spectra were recorded on Perkin-Elmer Lambda 40 spectrophotometer. Elemental microanalyses were carried out at the Microanalytical Laboratory of Cairo University, Giza, Egypt.

### Synthesis of Thiadiazoles (3a–e)

**Method A.** An equimolar amount of the appropriate 1,3,4-thiadiazoline derivatives **1** (5 mmol,) and 2-adamantanone **2** (0.75 g, 5 mmol) in absolute EtOH (40 mL) were refluxed for 6 h. The resulting solids were collected by cooling and crystallized from EtOH/DMF to give the final product **3**.

**Method B.** To a solution of hydrazonoyl bromides **5** (5 mmol) and methyl 2-(adamantan-2-ylidene)hydrazinecarbodithioate **4** (1.27 g, 5 mmol) in 10 mL DMF, 30 mL EtOH, was added triethylamine (TEA) (5 mmol, 0.7 mL), and the mixture was refluxed for 5 h monitored by TLC. The resulting solids were collected and recrystallized from EtOH/DMF to give the final products **3**.

**2-(Adamantan-2-ylidenehydrazono)-3-(4-bromophenyl),5-(4-methoxyphenyl)-2,3-dihydro-1,3,4-thiadiazole (3a):** Yellow brown crystalline solid from EtOH/DMF, Yield (78%); mp 171 °C; IR ( $\text{cm}^{-1}$ ) (KBr): 3079, 3045 (C-H Ar), 1605 (C=N);  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ ): 1.80 (10H, adam), 2.09 (4H, adam), 3.69 (s, 3H, OCH<sub>3</sub>), 6.87-8.02 (m, 8H, ArH) ppm. MS  $m/z$  (%): 508 ( $\text{M}^+$ , 75); Anal. Calcd for  $\text{C}_{25}\text{H}_{25}\text{BrN}_4\text{OS}$  (509.46): C, 58.94; H, 4.95; N, 11.00. Found: C, 58.91; H, 4.97; N, 11.03.

**2-(Adamantan-2-ylidenehydrazono)-3-(4-bromophenyl)-5-(4-tolyl)-2,3-dihydro-1,3,4-thiadiazole (3b):** Yellow brown crystalline solid from EtOH/DMF, Yield (84%); mp 177 °C; IR ( $\text{cm}^{-1}$ ) (KBr): 3089,

3055 (C-H Ar), 1610 (C=N);  $^1\text{H}$  NMR (DMSO- $d_6$ ): 1.85 (10H, adam), 2.07 (4H, adam), 2.39 (s, 3H, CH<sub>3</sub>), 7.15-8.24 (m, 8H, ArH) ppm. MS  $m/z$  (%): 492 (M<sup>+</sup>, 57); Anal. Calcd for C<sub>25</sub>H<sub>25</sub>BrN<sub>4</sub>S (492.1): C, 60.85; H, 5.11; N, 11.35. Found: C, 60.81; H, 5.14; N, 11.31.

**2-(Adamantan-2-ylidenehydrazono)-3-(4-bromophenyl),5-(phenyl)-2,3-dihydro-1,3,4-thiadiazole**

**(3c):** Yellow brown crystalline solid from EtOH/DMF, Yield (79%); mp 220 °C; IR (cm<sup>-1</sup>) (KBr): 3088, 3051 (C-H Ar), 1613 (C=N);  $^1\text{H}$  NMR (DMSO- $d_6$ ): 1.88 (10H, adam), 2.06 (4H, adam), 7.39-8.01 (m, 9H, ArH) ppm. MS  $m/z$  (%): 478 (M<sup>+</sup>, 75); Anal. Calcd for C<sub>24</sub>H<sub>23</sub>BrN<sub>4</sub>S (478.08): C, 60.12; H, 4.84; N, 11.69. Found: C, 60.11; H, 4.81; N, 11.63.

**2-(Adamantan-2-ylidenehydrazono)-3-(4-bromophenyl),5-(4-chlorophenyl)-2,3-dihydro-1,3,4-thiadiazole**

**(3d):** Yellow brown crystalline solid from EtOH/DMF, Yield (82%); mp 186 °C; IR (cm<sup>-1</sup>) (KBr): 3079, 3045 (C-H Ar), 1616 (C=N);  $^1\text{H}$  NMR (DMSO- $d_6$ ): 1.85 (10H, adam), 2.09 (4H, adam), 7.43-8.09 (m, 8H, ArH) ppm. MS  $m/z$  (%): 512 (M<sup>+</sup>, 75); Anal. Calcd for C<sub>24</sub>H<sub>22</sub>BrClN<sub>4</sub>S (512.04): C, 56.09; H, 4.32; N, 10.90. Found: C, 56.05; H, 4.36; N, 10.94.

**2-(Adamantan-2-ylidenehydrazono)-3,5-(di-(4-bromophenyl))-2,3-dihydro-1,3,4-thiadiazole**

**(3e):** Pale yellow crystalline solid from EtOH/DMF, Yield (88%); mp 146 °C; IR (cm<sup>-1</sup>) (KBr): 3089, 3055 (C-H Ar), 1610 (C=N);  $^1\text{H}$  NMR (DMSO- $d_6$ ): 1.83 (10H, adam), 2.06 (4H, adam), 7.72-8.11 (m, 8H, ArH) ppm. MS  $m/z$  (%): 555 (M<sup>+</sup>, 75); Anal. Calcd for C<sub>24</sub>H<sub>22</sub>Br<sub>2</sub>N<sub>4</sub>S (555.99): C, 51.63; H, 3.97; N, 10.03. Found: C, 51.61; H, 3.94; N, 10.07%.

**Synthesis of Bisthiadiazoles (7).** An equimolar amount of the appropriate 1,4-diphenylterephthalohydrazonoyl dichloride **6** (5 mmol, 1.91 g) and methyl 2-(adamantan-2-ylidene)hydrazinecarbodithioate **4** (5 mmol, 1.635 g) in EtOH/DMF (30/10 mL) was added triethylamine (10 mmol, 1.4 mL), were refluxed for 11 h. The solvent evaporated and the residue triturated with MeOH. The formed solid filtered and recrystallized from EtOH/DMF to give compounds **7**.

**1,4-Bis-(5-(adamantan-2-ylidenehydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)benzene**

**(7):** Brown from EtOH/DMF; Yield (87%); mp > 300 °C; IR (KBr): 3089, 3055 (C-H Ar), 1601 (C=N);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ): 1.85 (12H, adam), 2.07 (16H, adam), 7.54-8.23 (m, 14H, ArH) ppm. MS  $m/z$  (%): 722 (18). Anal. Calcd for C<sub>42</sub>H<sub>42</sub>N<sub>8</sub>S<sub>2</sub> (722.30): C, 69.77; H, 5.86; N, 15.50. Found: C, 69.72; H, 5.83; N, 15.53%.

**Synthesis of Thiadiazoles (10 and 11).** An equimolar amount of the appropriate 2,5-dihydrazinyl-1,3,4-thiadiazole **8** (5 mmol) and 2-adamantanone **2** or acetylferrocene **9** (2.28 g, 10 mmol) in absolute EtOH (40 mL) were refluxed for 10 h. The resulting solids were collected by cooling and crystallized from EtOH/DMF to give **10** and **11**.

**2,5-Bis(2-(adamantan-2-ylidene)hydrazinyl)-1,3,4-thiadiazole (10):** Yellow solid; Yield (79%); mp > 300 °C. IR (KBr):  $\nu_{\max}$  3165 (NH), 1595 (C=N)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (DMSO- $d_6$ ): 1.84 (12H, adam), 2.13 (16H, adam), and 10.75 (s, 2H, NH) ppm. MS  $m/z$  (%): 410 ( $\text{M}^+$ , 51). Anal. Calcd for  $\text{C}_{22}\text{H}_{30}\text{N}_6\text{S}$  (410.58): C, 64.36; H, 7.36; N, 20.47. Found: C, 64.31; H, 7.32; N, 20.49%.

**2,5-Bis(2-(1-(ferrocenylidene)hydrazinyl)-1,3,4-thiadiazole (11):** Red brown solid; Yield (85%); mp 165 °C. IR (KBr):  $\nu_{\max}$  3220 (NH), 1596 (C=C),  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (DMSO- $d_6$ ): 2.51 (s, 6H, 2 $\text{CH}_3$ ), 4.12 (m, 10H, 2 $\text{C}_5\text{H}_5$ ), 4.69 (m, 8H, 2 $\text{C}_5\text{H}_4$ ), and 10.88 (s, 2H, NH) ppm. MS  $m/z$  (%): 566 ( $\text{M}^+$ , 64); Anal. Calcd for  $\text{C}_{26}\text{H}_{26}\text{Fe}_2\text{N}_6\text{S}$  (566.06): C, 55.15; H, 4.63; N, 14.84. Found: C, 55.13; H, 4.66; N, 14.81%.

**Synthesis of poly(benzylidenehydrazinyl-1,3,4-thiadiazole) (14).** Equimolar quantities of 2,5-dihydrazinyl-1,3,4-thiadiazole **8** and terephthalaldehyde **12** were heated under reflux condition in DMF solvent. After 15 min, the system was connected to a vacuum pump and the azeotrope was distilled out. The contents were heated in an oil bath with magnetic stirrer at 140 °C for 72 h. The contents were poured into water along with stirrer and the precipitated poly(benzylidenehydrazinyl-1,3,4-thiadiazole) was filtered, washed with hot water and finally with EtOH.

The IR spectrum of the polymer **14** observed at 3169 (NH), 1610 (C=N)  $\text{cm}^{-1}$ . The  $^1\text{H}$  NMR were appeared aromatic protons of the polymer as a broad signal in the region 7.24–7.64 (m, ArH's) ppm, the –CH=N protons appeared at  $\delta$  8.09 ppm and the NH protons at  $\delta$  10.04 (s, NH) ppm. The  $^{13}\text{C}$  NMR spectrum observed at  $\delta$  129.57, 130.11, 139.67 and 158.64 ppm.

**Poly(benzylidenehydrazinyl-1,3,4-thiadiazole) (14):** Yellow solid; Yield (79%); mp > 300 °C. IR (KBr):  $\nu_{\max}$  3169 (NH), 1610 (C=N)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (DMSO- $d_6$ ): 7.24–7.64 (m, ArH's), 8.09 (s, –CH=N) and 10.04 (s, NH) ppm. The  $^{13}\text{C}$  NMR spectrum of polymer appeared at  $\delta$  129.57, 130.11, 139.67 and 158.64 ppm.

**Synthesis of poly[1,3,4]thiadiazolo[2,3-*c*:5,4-*c'*]bis([1,2,4]triazines) (17).** To 2,5-dihydrazinyl-1,3,4-thiadiazole **8** (5 mmol, 0.73 g) and *N*-(4-((4-(2-(1-chloro-2-oxopropylidene)hydrazinyl)phenyl)sulfonyl)phenyl)-2-oxopropanehydrazonoyl chloride **15** (10 mmol) in

dioxane (50 mL) was added triethylamine (1.4 mL, 10 mmol) at room temperature. The reaction mixture was heated under reflux until all the starting materials were consumed (10 h, monitored by TLC). The solvent was evaporated and the residue was triturated with MeOH. The formed solid was filtered and recrystallized from DMF to give compounds **17**.

**Poly[1,3,4]thiadiazolo[2,3-*c*:5,4-*c'*]bis([1,2,4]triazines) (17):** Brown solid from DMF; Yield (73%); mp 177 °C; IR (cm<sup>-1</sup>) (KBr): 3210 (s, 2H, NH), 1605 (C=N); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 2.61 (s, 6H, CH<sub>3</sub>), 7.26–8.07 (m, ArH's), and 11.67 (s, NH) ppm.

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